ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2022 December 28; 28(48): 6791-6961

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
December 28, 2022

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World J Gastroenterol 2022 December 28; 28(48): 6888-6899

DOI: 10.3748/wjg.v28.i48.6888

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Current status of novel biologics and small molecule drugs in the individualized treatment of inflammatory bowel disease

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ghaffar KA, Egypt; Knudsen T, Denmark

Received: September 13, 2022
Peer-review started: September 13, 2022
First decision: November 5, 2022
Revised: November 11, 2022
Accepted: December 1, 2022
Article in press: December 1, 2022
Published online: December 28, 2022

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Abstract

Treatment strategies for inflammatory bowel disease (IBD) are rapidly evolving with the development of biologics and small molecule drugs (SMDs). However, these drugs are not guaranteed to be effective in all patients, and a "ceiling effect" of biologic monotherapy may occur. This issue highlights an unmet need for optimizing the use of biologics and predicting therapeutic responses. Thus, the development of new drugs with novel mechanisms of action is urgently needed for patients with primary nonresponse and secondary loss of response to conventional biologics and SMDs. In addition, combining different biologics or SMDs has been proposed as a novel strategy to enhance treatment efficacy in IBD, which theoretically has multidimensional anti-inflammatory potential. Based on the current evidence available for IBD, dual targeted therapy may be a promising strategy for refractory IBD patients who have failed in multiple biologic treatments or who have extraintestinal manifestation. Additionally, identifying the subgroup of IBD patients who are responding to biological combination therapies is also equally important in stable disease remission. In this review, we summarize the newly developed biologics and SMDs and the current status of biologics/SMDs to highlight the development of individualized treatment in IBD.

Key Words: Inflammatory bowel diseases; Biologic; Dual targeted therapy; Therapeutic drug monitoring; Bispecific antibodies

Core Tip: The emergence of biologics and small molecules has significantly changed the therapies used for inflammatory bowel disease (IBD). However, the efficacy of these drugs is not satisfactory for every patient, which indicates an unmet need for optimizing the use of biologics/small molecules and for predicting therapeutic responses. Here, we describe the current status of novel biologics and small molecules and new treatment strategies to combat IBD by using more than one biologic.

Citation: Xu YH, Zhu WM, Guo Z. Current status of novel biologics and small molecule drugs in the individualized treatment of inflammatory bowel disease. *World J Gastroenterol* 2022; 28(48): 6888-6899
URL: https://www.wjgnet.com/1007-9327/full/v28/i48/6888.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i48.6888

INTRODUCTION

The inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's disease (CD) are progressive inflammatory diseases with the gastrointestinal tract being the major site of inflammation. Patients require lifelong medical therapy in the context of the complicated aetiology of IBD[1]. Encouragingly, the advent of biologics and small molecule drugs (SMDs) has fundamentally changed patient prognoses and improved their quality of life. Strong evidence has indicated that early treatment with these drugs might lead to more favorable outcomes, such as deeper inflammation control and longer steroid-free remission[2]. Despite the optimization of biological therapies, the proportion of patients who exhibit primary nonresponse and secondary loss of response to biologics remains high, and approximately only 40% of patients who respond to biologic therapies maintain clinical remission in one year[3]. This highlights a potential "ceiling effect" of biological monotherapy and an unmet need for optimizing the use of biologics and for predicting therapeutic responses. Thus, patients need not only new drugs but also optimized treatment strategies. In the last decade, increasing numbers of new biologics and SMDs have been developed for IBD treatment[4], and a novel therapy combining different biologics and/or SMDs targeting multiple inflammatory signalling pathways, which is called dual targeted therapy (DTT), has begun to emerge in recent years[5]. However, whether DTT is superior to monotherapy in achieving the new target of long-term deep healing is uncertain. Additionally, DTT might only work in a selected subgroup of IBD patients, and indiscriminate use of DTT is expensive, ineffective, and unsafe [6]. Thus, in the era of biologics, it is important to identify eligible patients and treat them with individualized therapy. In this review, we describe newly emerging drugs and advanced strategies to provide insight for optimizing the current treatments for IBD in the context of individualized medicine.

EMERGING BIOLOGICS AND SMDS IN IBD

Currently, the goal of IBD treatment is not only to maintain clinical remission but also to achieve transmural healing to prevent further structural damage. Therefore, biologics and/or SMDs are recommended for patients with moderate to severe IBD. To date, the approved biological and small molecule therapies for IBD consist of the following anti-tumor necrosis factor (TNF) agents [infliximab (IFX), adalimumab (ADA), certolizumab (CZP), golimumab (GOL)], anti-adhesion agents [vedolizumab (VDZ), natalizumab (NAT)], anti-interleukin (IL)-12/23 agents [ustekinumab (UST)], and Janus kinase (JAK) inhibitors (tofacitinib). However, the current biological monotherapies are efficacious only in a certain proportion of patients. For example, only 30%-50% of active patients can achieve clinical or mucosal remission after biological inducing therapy. Besides, the rates of long-term corticosteroid-free remission are even lower and are less than 30%[7]. Thus, new drug development is rapidly advancing to meet the needs of patients with primary nonresponse, loss of response or intolerance to conventional biologics and SMDs (Table 1).

Anti-TNF agents

Anti-TNF agents were the first class of biologics to be approved for IBD treatment, and since then, they have tremendously changed IBD management. However, even in patients who respond to anti-TNF agents, the scope of anti-TNF use is limited due to systemic effects, such as infection and immunosuppression[8]. In addition, immunogenicity is another complex problem in anti-TNF-based treatment. Although some randomized controlled trials (RCTs) have shown that adding immunomodulators (IMs), such as the thiopurines azathioprine and 6-mercaptopurine, may reduce the immunogenicity of anti-TNF agents, and then improve the efficacy of anti-TNF therapy, only a minority of patients will benefit from this strategy[9,10]. Gut-selective anti-TNF agents might overcome these defects. An oral anti-TNF agent is currently in development. Since the antibodies comprising this therapy are derived from cow

Table 1 Summary of emerging biologics and small molecule drugs in inflammatory bowel disease treatments

Drug class	Agent	Target	Route	IBD type	Ref.
Anti-TNF	AVX470	Anti-TNF	Oral	UC	[11]
Anti-IL-23	Risankizumab	IL-23/p19 subunit	IV/SC	CD/UC	[17]
	Brazikumab	IL-23/p19 subunit	IV/SC	CD/UC	[15]
	Mirikizumab	IL-23/p19 subunit	IV/SC	CD/UC	[18]
	Guselkumab	IL-23/p19 subunit	IV/SC	CD/UC	[16]
Anti-lymphocyte trafficking	Etrolizumab	α4β7 and αEβ7 integrins	SC	CD/UC	[22]
	AJM300	α4 integrin	Oral	UC	[23]
	Ontamalimab	MAdCAM	SC	CD/UC	[38]
S1P receptor modulators	Ozanimod	S1PR1 and S1PR5	Oral	CD/UC	[24]
	Etrasimod	S1PR1, S1PR4 and S1PR5	Oral	CD/UC	[39]
JAK inhibitor	Filgotinib	JAK1	Oral	CD/UC	[27]
	Upadacitinib	JAK1	Oral	CD/UC	[28]
PDE4 inhibitor	Apremilast	PDE4	Oral	CD/UC	[30]

Anti-TNF: Anti-tumour necrosis factor; CD: Crohn's disease; IBD: Inflammatory bowel disease; IL-23: Interleukin-23; IV: Intravenous; MAdCAM: Mucosal addressin cell adhesion molecule-1; PDE4: Phosphodiesterase 4; SC: Subcutaneous; SMDs: Small molecule drugs; SIP: Sphingosine-1-phosphate; UC: Ulcerative colitis.

colostrum, this agent can act on the small intestine and colon in a delayed-release manner. A preclinical study that assessed the efficacy of AVX-470 showed a higher clinical response rate in the treatment group at week 4 than in the control group (25.9% *vs* 11.1%)[11]. Additionally, serious systemic side effects and formation of anti-drug antibodies were not observed. The current new oral formulation of anti-TNF agents might bring gut specificity to anti-TNF treatments. However, many more clinical studies are needed to confirm the efficacy of this novel formulation.

Anti-IL-12/23 agents

IL-12/23 signalling pathways are the key in regulating the differentiation and maturation of Th17 cells, which results in intestinal inflammation in IBD[12]. The conventional anti-IL-12/23 agent, UST, prevents activation of the IL-12/23 signalling pathway by targeting the shared subunit of cytokine p40 of IL-23 and IL-12[13,14]. At present, several monoclonal antibodies are in development that targets other subunits of IL-12/23.

Briakinumab is a human monoclonal antibody that acts specifically against the p19 subunit of IL-23 and exerts no effect on IL-12. In a clinical phase II study, 119 CD patients who failed anti-TNF therapy received brazikumab or placebo randomly at the beginning of the trial and 4 wk later. A higher clinical response rate was observed in brazikumab-treated patients than for those in the placebo group (49% *vs* 27%, $P = 0.01$)[15]. Guselkumab is another anti-p19 human mAb that was assessed in a phase II study in 250 patients with moderate-to-severe CD. Patients in all guselkumab groups treated with different doses exhibited a significant reduction in inflammatory activity at week 12. In addition, more patients in guselkumab treatments achieved clinical response [200 mg: 54%, 600 mg: 65%, 1200 mg: 50% *vs* 15.7% placebo ($P < 0.001$, respectively)] and safety events were similar between the groups[16]. Risankizumab, another anti-p19 monoclonal antibody, resulted in a 31% remission rate in treated CD patients in a phase III study, which was much higher than that in the control group (15%)[17]. Similarly, another anti-p19 antibody, mirikizumab, seemed to be effective in inducing remission in patients with moderate to severe UC[18]. Inhibition of the IL-12/23 signalling pathway is a promising therapeutic option for IBD, especially if the safety of the new anti-IL-12/23 agents targeting the p19 subunit can be confirmed.

Anti-lymphocyte trafficking agents

Inhibition of immune cell migration to inflamed tissue has emerged as a novel therapeutic mechanism for IBD[19]. VDZ is the most commonly used antiadhesion agent with a selective blocking effect of the α 4β7 integrin in the intestine[20]. In addition to this agent, etrolizumab is a newly developed monoclonal antibody that targets the β7 subunit of the α4β7 and αEβ7 integrins. In a study that included 1081 patients with moderate to severe UC, the rate of remission induction in the etrolizumab group was 18.5% compared with only 6.3% in the placebo group[21]. Etrolizumab was also reported to be effective in CD patients[22]. In addition, inhibition of the integrin-α4 subunit might also be useful for inflam-

mation control in IBD. AJM300 is a small molecule inhibitor of the α4 subunit of integrin that led to disease remission rate of 63% compared with a 26% remission rate in the placebo group among 102 UC patients in a randomized controlled study[23]. Another mechanism that limits immune cell migration is the inhibition of the sphingosine-1-phosphate receptor (S1PR). The S1P signalling network is mediated by 5 S1P G-protein coupled receptors (S1PR1-5). Ozanimod is a new class of S1PR modulators that shows activity against S1PR1 and S1PR5. In the TOUCHSTONE study, ozanimod therapy showed excellent efficacy in remission induction and maintenance in moderate to severe UC, and mucosal healing was better (34% with ozanimod *vs* 12% with placebo)[24]. Anti-lymphocyte migration might be an attractive therapeutic strategy in some situations, and these drugs may be promising and powerful in IBD management.

JAK inhibitors

The JAK family comprises important intracellular signalling molecules consisting of 3 subtypes (*e.g.*, JAK1, JAK2, and JAK3). Tofacitinib is the only SMD targeting JAK1 and JAK3 for moderate to severe UC that is approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA)[25]. However, some studies have revealed an association between tofacitinib and systemic side effects, such as malignancies, cardiovascular events, and venous thromboembolism, in patients with rheumatoid arthritis[26]. Thus, more selective JAK inhibitors are needed for IBD. Currently, filgotinib is a selective JAK1 inhibitor that has shown promising effects in the induction of disease remission in CD patients in the phase II FITZROY study[27]. More patients treated with filgotinib achieved endoscopic response, remission and healing compared with those who received placebo (47% *vs* 23%, $P = 0.0077$). However, data from that study showed that patients in the filgotinib group experienced more serious adverse events (9% *vs* 4%) and more serious infections (3% *vs* 0%) than those in the placebo group. Upadacitinib is another oral selective JAK1 inhibitor. The CELEST trial recently assessed upadacitinib in patients with moderate to-severe CD. At week 16, clinical remission was notable in the 6 mg group (upadacitinib 27% *vs* 11% placebo, $P < 0.1$). However, at week 52, patients in the upadacitinib groups had a higher incidence of serious infections. In addition, patients treated with 12 or 24 mg twice daily had increased serum lipids[28]. Generally, these new selective JAK inhibitors provide a promising prospects in IBD treatments, but their safety profiles should not be ignored.

Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 (PDE4) is involved in intracellular cAMP transformation and activation of the nuclear transcription factor kappaB and promotes inflammation in the intestine[29]. Thus, PDE4 inhibition may reduce cytokine release syndrome. A phase II RCT assessed the efficacy of the PDE4 inhibitor apremilast in 170 adult UC patients. The results showed a higher clinical remission rate in patients treated with apremilast *vs* placebo[30]. In addition, significant decreases in inflammatory markers, such as C-reactive protein (CRP) and faecal calprotectin, were observed in this study.

Taken together, although the understanding of the pathogenesis of IBD is rapidly evolving and increasing numbers of new biologics and SMDs that have been developed, none of these drugs is effective in all patients. Thus, there is increasing interest in the therapeutic potential of the combination of biologics and/or SMDs with different mechanisms of action in patients with refractory IBD.

THE CURRENT STATUS OF BIOLOGICAL COMBINATIONS IN IBD

The immune response in IBD is multifaceted and accompanied by multiple activated inflammatory pathways in the intestinal mucosa. Single-targeted therapy consisting of biological monotherapy blocks only one inflammatory pathway, which is inadequate to control inflammation completely. Combinations of biologics with different mechanisms may have synergistic effects and contribute to the control of refractory IBD[3,31]. Currently, an emerging strategy, DTT, which is a combination of two biologics or a biologic and tofacitinib has been applied in patients with refractory disease. However, most studies on DTT are case reports and case series, and therefore, we could not summarize data to provide a comprehensive understanding of experiences with this strategy. From the limited evidence available, we briefly discuss the current paradigms of DTT in treating patients with refractory IBD who have failed multiple biologics.

As a prominent anti-TNF biologic, IFX was the first biologic agent used in IBD and has achieved great success[20]. In the last decade, several RCTs have demonstrated the efficacy of IFX combined with immunosuppressive agents[9,32,33]. However, approximately one-third of IBD patients exhibit no response to anti-TNF biologics, and another third need to switch to different agents within one year due to the secondary loss of response[20,34]. With the permission of the FDA and EMA, VDZ has become the first choice among second-line biologics for moderate to severe CD and UC patients who have experienced failure with conventional medications or anti-TNF agents[31]. Thus, in clinical practice, anti-TNF + VDZ is the most common combination paradigm used in DTT. A meta-analysis consisting of 30 studies of dual biologics or SMDs in IBD management revealed that the proportion of anti-TNF + VDZ algorithms ranked first among the various DTT paradigms and accounted for 48% of all

algorithms used. The combination of UST + VDZ was the second most popular paradigm and accounted for 19%. The clinical response rates and endoscopic response rates were comparable for different DTT groups in this meta-analysis[35]. Yang *et al*[36] reported that the rates of endoscopic improvement [reduction of simple endoscopic score for CD (SES-CD) > 50%] for anti-TNF + VDZ and anti-TNF + UST were both 33%. Additionally, VDZ + UST had the highest rates of endoscopic improvement (63%) compared with other combinations, but all DTT paradigms had similar efficacy in terms of endoscopic remission (SES-CD < 3). To date, the broadest experience with IBD patients treated with various DTTs is reported by a retrospective study[37]. Fifty patients with IBD [31 CD, 18 UC and 1 IBD-unclassified (IBD-U)] were included in this study. VDZ + UST was the most used combination paradigm (25/50), followed by VDZ + ADA (3/50), VDZ + GOL (2/50), and VDZ + CZP (2/50). Notably, 20 patients received tofacitinib combined with biologic treatment, but no specific data on this subgroup were provided in this report. The results from this study showed that CRP levels were significantly reduced from baseline (2.35 mg/dL *vs* 5.00 mg/dL, $P = 0.002$), 56% (18/32) of patients treated with dual biologic therapy maintained clinical remission after 3 mo, and that 11 of 32 patients were still in endoscopic remission after 8 mo[37]. Currently, growing numbers of newer biologics and SMDs are included in the candidate pools for DTTs, including anti-IL-23 agents such as mirikizumab, risankizumab, brazikumab and guselkumab, anti-integrin agents such as etrolizumab and ontamalimab [38], new SMDs such as PDE-4 inhibitors, as well as IL-6 inhibitors and S1PR agonists[4,39,40].

Although the use of DTTs that address different targets is increasingly applied to treat patients with refractory CD or UC, no strong evidence has shown that DTT might be effective in all patients. An early RCT included 79 patients with active CD who failed to respond to IFX treatment and did not report a statistically significant difference in efficacy between the IFX + NAT group and the IFX + placebo group [41]. Another observational study conducted on 16 paediatric patients with refractory IBD (7 CD, 9 UC, 1 IBD-U) showed that 75% achieved steroid-free clinical remission 6 mo after DTT but that 19% of patients discontinued DTT treatment because of inflammation control failure[42]. Additionally, some low-quality evidence suggested that DTT is more effective in CD patients with a penetrating phenotype [36,43]. Among the patients enrolled in a study conducted by Kwapisz *et al*[43], the median disease duration was 12.5 years, 86.7% (13/15) had penetrating disease, and 3.8 types of biologics were ineffective for these patients. Despite the disease severity, more than half of patients exhibited improved clinical symptoms and had less steroid use after DTT[43]. However, it is still unclear which combinations of biologics work best in specific IBD subgroups. Understanding of the pathophysiology of IBD and identifying prognostic biomarkers may significantly optimize DTT therapy.

WHAT CAN WE DO TO IMPROVE THE RESPONSE TO DTT

Heterogeneity among patients is one of the main features of IBD and is reflected by different disease behaviors and responses to therapeutics[44]. Although remarkable progress has been achieved in the development of new agents with novel mechanisms of action assisted by advanced management strategies, the current treatment pattern for IBD still relies on clinical symptoms and endoscopy examinations[45]. In addition, as mentioned above, many drugs are effective only in selected patients with IBD, and even DTT strategies cannot guarantee a response in all patients. Thus, the identification of patients who can benefit from DTT is urgent so that individualized treatment with biological agents can be provided.

Therapeutic drug monitoring enhanced the response to DTT

DTT is mainly used as an add-on therapy for patients who exhibit a partial response to monotherapy or who relapse during maintenance therapy. A major problem associated with failure of biological therapy is a loss of response, and therapeutic drug monitoring (TDM) may be a useful auxiliary tool in the management of patients treated with DTT[6,46].

TDM was originally suggested as a way to monitor the response to monotherapy and is divided into two categories: Proactive TDM (performed regularly to target an appropriate drug trough concentration) and reactive TDM (performed upon loss of response)[46]. Strong evidence indicates that TDM implementation is associated with higher rates of clinical remission, better endoscopic mucosal healing, and lower rates of secondary loss of response to biologics[47,48]. To date, TDM has achieved great success in optimizing the management of a combined biologics approach in patients treated with anti-TNF agents. The most convincing evidence comes from the management of secondary failures for IFX and ADA. The personalized anti-TNF therapy in CD study (PANTS), which included 1610 anti-TNF-naive patients with exposure to IFX or ADA, demonstrated that monitoring drug concentrations helps greatly in predicting therapeutic responses. The results showed that the only risk factor associated with primary nonresponse was low drug concentrations at week 14 [IFX: Odds ratio (OR) = 0.35, 95% confidence interval (CI): 0.20-0.62, $P = 0.00038$; ADA: OR = 0.13, 95%CI: 0.06-0.28, $P < 0.0001$] and that ideal drug concentrations at week 14 (7 mg/L for IFX and 12 mg/L for ADA) were a strong predictor for clinical remission at week 54. With the guidance of proactive TDM, dose intensification of initial biologics or combinations with IM (thiopurine or methotrexate) therapy improved outcomes of patients

with suboptimal drug concentrations at week 14[47]. Additionally, an expert consensus statement by Cheifetz *et al*[49] recommended a proactive TDM strategy during remission induction with anti-TNF agents and at least once during maintenance.

Reactive TDM could help distinguish patients who need to switch or combine with another class of biologic due to anti-drug antibodies (immunogenicity) from those who might benefit from dose escalation of monotherapy[50]. Actually, identifying patients with pharmacokinetic failure in biologics therapy is extremely useful in the guidance of biologics regimens, especially in DTT. Inadequate trough concentrations of drugs can not only lead to an insufficient efficacy of biologics, but patients may also become insensitive to the mechanism of action. For example, it was recently found that anti-TNF resistance in CD patients may be related to increased numbers of CD4+ T cells that overexpress the IL-23 receptor. Thus, it is possible that combinations with IL-23 inhibitors may help restore the sensitivity to the mechanism of action of anti-TNFs in such patients[51].

At present, there is little research focusing on the role of TDM for biologics other than anti-TNF agents, such as VDZ (anti-α4β7 integrin) or UST (anti-IL-12/23)[52]. Although the relationship between drug concentrations and clinical outcomes has been demonstrated, the value and cost-effectiveness of TDM in optimizing these biologic therapies are uncertain, and all the information given regarding TDM is derived from studies performed in patients treated with monotherapy. Therefore, relevant guidelines about TDM implementation in DTT have not been recommended by any academic association. Overall, TDM has great value in optimizing biologics therapy and providing individualized treatment for IBD but still has very significant problems and challenges in clinical practice.

Biomarkers help predict responses to biological therapies

IBD treatments are a long-term process, and disease monitoring is essential once treatment has started. A growing number of studies have put great effort into identifying prognostic and predictive biomarkers[53,54]. To date, various biomarkers have been proposed as clinical predictors of the response to biologics, including serological and faecal proteins, cytokines, proteomic-related and microbiome-related factors as well as metabolomic and genetic factors[55].

Serum and faecal markers have been widely applied in evaluating the efficacy of biologics. Serum CRP and fecal calprotectin, as inflammatory markers, have been shown helpful in response detection of anti-TNF agents. Although fecal markers are more sensitive than serum markers, such as CRP, in monitoring intestinal inflammation, there is no solid evidence demonstrating the association between fecal biomarkers and the response to anti-TNF agents[56,57]. Some proteins in the intestinal mucosa can also play a predictive role in response to biologics, such as Piwi-like protein 1, MYCBP associated and testis expressed 1, regulators of G-protein signaling 13 and Dachsous 2. Elevated expressions of these cytokines or proteins are beneficial for achieving a stable response to anti-TNF therapy[58,59].

Exploration of the genetic factors that predict the responses to anti-TNF therapy has also made great progress. The genetic polymorphisms in TNFRSF1A (rs4149570), IL-6 (rs10499563), IL-1β (rs4848306), toll-like receptors 2 (TLR2) (rs3804099), and TLR4 (rs5030728) are associated with the response to anti-TNF agents[60]. In addition, an observational study including 1240 European patients with CD found that the human leukocyte antigen-DQA1*05 mutation increased the risk of developing anti-TNF antibodies[61]. Single-cell sequencing revealed that some activated cells [*e.g.*, macrophages, immunoglobulin G (IgG) cells, T cells, and dendritic cells] in patients with failure to receive anti-TNF therapy are dysfunctional with genetic variation[62].

Many studies have suggested that the composition of the gut microbiota is related to the response to therapies. In the STORI study, Rajca *et al*[63] found that lower levels of *Faecalibacterium prausnitzii* (*F. prausnitzii*) were associated with early recurrence of CD after IFX withdrawal. Additionally, higher abundances of *F. prausnitzii* were associated with better responses to anti-TNF treatments[64,65]. Nevertheless, this relationship could not be confirmed in other studies[66], and when we examine the effects of other bacteria, studies with conflicting results are common[65,67]. To date, the microbiome has not been shown to be a predictive indicator of the response to biologics due to the very high heterogeneity in different individuals.

Metabolomics is a novel method that can quantify small metabolite sugars, such as lipids and amino acids, and thus offers a promising opportunity to identify candidate markers. Through metabolomic analysis, Nikolaus *et al*[68] found that the serum tryptophan levels increased in IBD patients who responded to IFX therapy but were unchanged in patients who did not respond to IFX or VDZ therapy. In addition, another study including 76 CD patients found that responders and non-responders have distinctive patterns of bile acids derived from feces, serum, and urine. By combining these representative markers, the responses to anti-TNFs may be predicted[69]. The biomarkers mentioned above could assist only with the accuracy of disease monitoring and response to biologics in IBD, and more studies are needed to identify a gold standard in the DTT strategy of IBD.

BISPECIFIC ANTIBODIES: THE NEXT GENERATION OF DTT

It has been proven that targeting multiple inflammatory signaling pathways by combining different

biologics has better outcomes for IBD patients than monotherapies[41,70]. However, the doses used in the DTT strategy are based on those for individual therapies, which might have unfavorable benefit-risk ratios, such as placing patients at greater risk of serious infections or malignancies[6,35]. The advent of bispecific antibodies (BsAbs) may provide new insights to help avoid some of these problems in DTT.

BsAbs are antibody formats that can bind to two different antigens or two different epitopes of the same antigen. Broadly, they can be classified as a special type of DTT. To date, BsAbs are divided into two major structural classes: IgG-like BsAbs carrying an Fc domain and non-IgG-like formats, which rely entirely on their antigen-binding capacity to exert therapeutic effects[71]. BsAbs can function by: (1) Impacting specific cell types by targeting multiple receptors; (2) Activating novel signaling *via* receptor colocalization or hyper crosslinking; and (3) Destroying pathogenic T cells through redirection[72]. Currently, different BsAbs are in different stages of clinical trials, and three BsAbs have been approved for clinical practice globally, namely, catumaxomab (for malignant ascites), blinatumomab (for leukemia) and emicizumab (for hemophilia)[71].

Although there are currently no BsAbs approved for IBD patients in clinical practice, several promising BsAbs are under investigation. For instance, BsAb drugs targeting both TNF and IL-23 are in the preclinical stage for autoimmune diseases, including IBD[72]. These BsAbs showed synergistic efficacy in alleviating colitis in a CD40-induced colitis model compared with anti-TNF and anti-IL-23 agents alone. Another ongoing phase I trial is investigating the effects of APVO210 in treating UC. These BsAbs are composed of an anti-CD86-IL-10 fusion protein and selectively deliver IL10 to CD68+ antigen-presenting cells, in which they have been demonstrated to induce a tolerogenic phenotype to relieve inflammation[73].

The unique mechanism of BsAbs provides an opportunity to target multiple molecular pathways with a single therapeutic agent. With careful dose adjustments, IBD patients can achieve maximal benefits from BsAbs and also good benefit-risk ratio[72]. However, this therapeutic approach is not without defects. On the one hand, the formulation of the two antibody binding domains of BsAbs is fixed, so it is impossible to change the single administration dose of different monoclonal antibodies according to patient needs, as we usually do in traditional dual biologic combination paradigms[74,75]. On the other hand, immunogenicity is an ever-present concern during the development of biological medication in IBD, especially in BsAbs. The large antibody complexes on the surface of BsAbs could act as "danger signals" that induce immunogenicity and eventually lead to loss of response[76].

CONCLUSION

Medical treatment patterns for IBD are rapidly evolving with the increased understanding of disease pathogenesis and development of new drugs that target various pathways. This review describes novel biological agents and SMDs that are in development and highlights the current status of DTT strategies in IBD management. Although drugs and therapeutic strategies that can cure all patients have not yet emerged, the efficacy of DTT in inducing and maintaining disease remission has been dramatically improved by taking advantage of new biological combination paradigms, modern TDM strategies, and novel predictive biomarkers. In future work, the identification of biomarkers that can predict subsets of patients and a more profound comprehension of the immunological landscape with IBD would help to enable more specific individualized medicine.

ACKNOWLEDGEMENTS

We sincerely appreciate Prof Yi Li (Jinling Hospital, Medical School of Nanjing University) for the help and suggestion in this article.

FOOTNOTES

Author contributions: Xu YH and Guo Z performed the majority of the writing and the table; Zhu WM designed the outline and coordinated the writing of the paper; and all authors have read and approve the final manuscript.

Supported by Jiangsu Provincial Health Commission, No. M2021013; and the Science Foundation of Jinling Hospital, No. YYMS2021035.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Verdon C**, Reinglas J, Coulombe J, Gonczi L, Bessissow T, Afif W, Vutcovici M, Wild G, Seidman EG, Bitton A, Brassard P, Lakatos PL. No Change in Surgical and Hospitalization Trends Despite Higher Exposure to Anti-Tumor Necrosis Factor in Inflammatory Bowel Disease in the Québec Provincial Database From 1996 to 2015. *Inflamm Bowel Dis* 2021; **27**: 655-661 [PMID: 32676662 DOI: 10.1093/ibd/izaa166]
2 **Ungaro RC**, Aggarwal S, Topaloglu O, Lee WJ, Clark R, Colombel JF. Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and paediatric patients with Crohn's disease. *Aliment Pharmacol Ther* 2020; **51**: 831-842 [PMID: 32202328 DOI: 10.1111/apt.15685]
3 **Hirten RP**, Iacucci M, Shah S, Ghosh S, Colombel JF. Combining Biologics in Inflammatory Bowel Disease and Other Immune Mediated Inflammatory Disorders. *Clin Gastroenterol Hepatol* 2018; **16**: 1374-1384 [PMID: 29481970 DOI: 10.1016/j.cgh.2018.02.024]
4 **Grossberg LB**, Papamichael K, Cheifetz AS. Review article: emerging drug therapies in inflammatory bowel disease. *Aliment Pharmacol Ther* 2022; **55**: 789-804 [PMID: 35166398 DOI: 10.1111/apt.16785]
5 **Haider M**, Lashner B. Dual Targeted Therapy for the Management of Inflammatory Bowel Disease. *J Clin Gastroenterol* 2021; **55**: 661-666 [PMID: 34238847 DOI: 10.1097/MCG.0000000000001583]
6 **Privitera G**, Pugliese D, Lopetuso LR, Scaldaferri F, Neri M, Guidi L, Gasbarrini A, Armuzzi A. Novel trends with biologics in inflammatory bowel disease: sequential and combined approaches. *Therap Adv Gastroenterol* 2021; **14**: 17562848211006669 [PMID: 33995579 DOI: 10.1177/17562848211006669]
7 **Song YN**, Zheng P. Efficacy and safety of tumor necrosis factor-α blockers for ulcerative colitis: A systematic review and meta-analysis of published randomized controlled trials. *J Food Drug Anal* 2015; **23**: 1-10 [PMID: 28911431 DOI: 10.1016/j.jfda.2014.06.003]
8 **Baumgart DC**, Le Berre C. Newer Biologic and Small-Molecule Therapies for Inflammatory Bowel Disease. *N Engl J Med* 2021; **385**: 1302-1315 [PMID: 34587387 DOI: 10.1056/NEJMra1907607]
9 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
10 **Panaccione R**, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, van Hoogstraten HJ, Chen AC, Zheng H, Danese S, Rutgeerts P. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014; **146**: 392-400.e3 [PMID: 24512909 DOI: 10.1053/j.gastro.2013.10.052]
11 **Almon E**, Shaaltiel Y, Sbeit W, Fich A, Schwartz D, Waterman M, Szlaifer M, Reuveni H, Amit-Cohen BC, Alon S, Chertkoff R, Paz A, Ilan Y. Novel Orally Administered Recombinant Anti-TNF Alpha Fusion Protein for the Treatment of Ulcerative Colitis: Results From a Phase 2a Clinical Trial. *J Clin Gastroenterol* 2021; **55**: 134-140 [PMID: 32501868 DOI: 10.1097/MCG.0000000000001314]
12 **Almradi A**, Hanzel J, Sedano R, Parker CE, Feagan BG, Ma C, Jairath V. Clinical Trials of IL-12/IL-23 Inhibitors in Inflammatory Bowel Disease. *BioDrugs* 2020; **34**: 713-721 [PMID: 33105016 DOI: 10.1007/s40259-020-00451-w]
13 **Feagan BG**, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P; UNITI–IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* 2016; **375**: 1946-1960 [PMID: 27959607 DOI: 10.1056/NEJMoa1602773]
14 **Sands BE**, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, Danese S, Targan S, Abreu MT, Hisamatsu T, Szapary P, Marano C; UNIFI Study Group. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2019; **381**: 1201-1214 [PMID: 31553833 DOI: 10.1056/NEJMoa1900750]
15 **Sands BE**, Chen J, Feagan BG, Penney M, Rees WA, Danese S, Higgins PDR, Newbold P, Faggioni R, Patra K, Li J, Klekotka P, Morehouse C, Pulkstenis E, Drappa J, van der Merwe R, Gasser RA Jr. Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study. *Gastroenterology* 2017; **153**: 77-86.e6 [PMID: 28390867 DOI: 10.1053/j.gastro.2017.03.049]
16 **Sandborn WJ**, D'Haens GR, Reinisch W, Panés J, Chan D, Gonzalez S, Weisel K, Germinaro M, Frustaci ME, Yang Z, Adedokun OJ, Han C, Panaccione R, Hisamatsu T, Danese S, Rubin DT, Sands BE, Afzali A, Andrews JM, Feagan BG; GALAXI-1 Investigators. Guselkumab for the Treatment of Crohn's Disease: Induction Results From the Phase 2 GALAXI-1 Study. *Gastroenterology* 2022; **162**: 1650-1664.e8 [PMID: 35134323 DOI: 10.1053/j.gastro.2022.01.047]
17 **Feagan BG**, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, Louis E, Franchimont D, Dewit O, Seidler U, Kim

KJ, Neurath MF, Schreiber S, Scholl P, Pamulapati C, Lalovic B, Visvanathan S, Padula SJ, Herichova I, Soaita A, Hall DB, Böcher WO. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2017; **389**: 1699-1709 [PMID: 28411872 DOI: 10.1016/S0140-6736(17)30570-6]

18 **Sandborn WJ**, Ferrante M, Bhandari BR, Berliba E, Feagan BG, Hibi T, Tuttle JL, Klekotka P, Friedrich S, Durante M, Morgan-Cox M, Laskowski J, Schmitz J, D'Haens GR. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis. *Gastroenterology* 2020; **158**: 537-549.e10 [PMID: 31493397 DOI: 10.1053/j.gastro.2019.08.043]

19 **Sandborn WJ**, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P; International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2) Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005; **353**: 1912-1925 [PMID: 16267322 DOI: 10.1056/NEJMoa043335]

20 **Katsanos KH**, Papamichael K, Feuerstein JD, Christodoulou DK, Cheifetz AS. Biological therapies in inflammatory bowel disease: Beyond anti-TNF therapies. *Clin Immunol* 2019; **206**: 9-14 [PMID: 29545207 DOI: 10.1016/j.clim.2018.03.004]

21 **Peyrin-Biroulet L**, Hart A, Bossuyt P, Long M, Allez M, Juillerat P, Armuzzi A, Loftus EV Jr, Ostad-Saffari E, Scalori A, Oh YS, Tole S, Chai A, Pulley J, Lacey S, Sandborn WJ; HICKORY Study Group. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7**: 128-140 [PMID: 34798039 DOI: 10.1016/S2468-1253(21)00298-3]

22 **Zhang W**, Scalori A, Fuh F, McBride J, She G, Kierkus J, Korczowksi B, Li R, Abouhossein M, Kadva A, Park KT, Tang MT. Pharmacokinetics, Pharmacodynamics, and Safety of Etrolizumab in Children With Moderately to Severely Active Ulcerative Colitis or Crohn's Disease: Results from a Phase 1 Randomized Trial. *Inflamm Bowel Dis* 2022; **28**: 1348-1356 [PMID: 34849918 DOI: 10.1093/ibd/izab275]

23 **Yoshimura N**, Watanabe M, Motoya S, Tominaga K, Matsuoka K, Iwakiri R, Watanabe K, Hibi T; AJM300 Study Group. Safety and Efficacy of AJM300, an Oral Antagonist of α4 Integrin, in Induction Therapy for Patients With Active Ulcerative Colitis. *Gastroenterology* 2015; **149**: 1775-1783.e2 [PMID: 26327130 DOI: 10.1053/j.gastro.2015.08.044]

24 **Sandborn WJ**, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, Ghosh S, Petersen A, Hua SY, Lee JH, Charles L, Chitkara D, Usiskin K, Colombel JF, Laine L, Danese S; True North Study Group. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2021; **385**: 1280-1291 [PMID: 34587385 DOI: 10.1056/NEJMoa2033617]

25 **Sandborn WJ**, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G, Lawendy N, Yu D, Woodworth D, Mukherjee A, Zhang H, Healey P, Panés J; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2017; **376**: 1723-1736 [PMID: 28467869 DOI: 10.1056/NEJMoa1606910]

26 **Fleischmann R**, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, DeMasi R, Soma K, Zhang R, Takiya L, Tatulych S, Mojcik C, Krishnaswami S, Menon S, Smolen JS; ORAL Strategy investigators. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet* 2017; **390**: 457-468 [PMID: 28629665 DOI: 10.1016/S0140-6736(17)31618-5]

27 **Vermeire S**, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, Klopocka M, Goldis A, Wisniewska-Jarosinska M, Baranovsky A, Sike R, Stoyanova K, Tasset C, Van der Aa A, Harrison P. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet* 2017; **389**: 266-275 [PMID: 27988142 DOI: 10.1016/S0140-6736(16)32537-5]

28 **Napolitano M**, D'Amico F, Ragaini E, Peyrin-Biroulet L, Danese S. Evaluating Upadacitinib in the Treatment of Moderate-to-Severe Active Ulcerative Colitis: Design, Development, and Potential Position in Therapy. *Drug Des Devel Ther* 2022; **16**: 1897-1913 [PMID: 35747444 DOI: 10.2147/DDDT.S340459]

29 **Kavanaugh A**, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, Lespessailles E, Hall S, Hochfeld M, Hu C, Hough D, Stevens RM, Schett G. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014; **73**: 1020-1026 [PMID: 24595547 DOI: 10.1136/annrheumdis-2013-205056]

30 **Karner M**, Kocjan A, Stein J, Schreiber S, von Boyen G, Uebel P, Schmidt C, Kupcinskas L, Dina I, Zuelch F, Keilhauer G, Stremmel W. First multicenter study of modified release phosphatidylcholine "LT-02" in ulcerative colitis: a randomized, placebo-controlled trial in mesalazine-refractory courses. *Am J Gastroenterol* 2014; **109**: 1041-1051 [PMID: 24796768 DOI: 10.1038/ajg.2014.104]

31 **Neurath MF**. Current and emerging therapeutic targets for IBD. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 269-278 [PMID: 28144028 DOI: 10.1038/nrgastro.2016.208]

32 **Schreiber S**, Ben-Horin S, Leszczyszyn J, Dudkowiak R, Lahat A, Gawdis-Wojnarska B, Pukitis A, Horynski M, Farkas K, Kierkus J, Kowalski M, Lee SJ, Kim SH, Suh JH, Kim MR, Lee SG, Ye BD, Reinisch W. Randomized Controlled Trial: Subcutaneous *vs* Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease. *Gastroenterology* 2021; **160**: 2340-2353 [PMID: 33676969 DOI: 10.1053/j.gastro.2021.02.068]

33 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095 DOI: 10.1056/NEJMoa050516]

34 **Singh S**, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. *J Crohns Colitis* 2018; **12**: 635-643 [PMID: 29370397 DOI: 10.1093/ecco-jcc/jjy004]

35 **Ahmed W**, Galati J, Kumar A, Christos PJ, Longman R, Lukin DJ, Scherl E, Battat R. Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2022; **20**: e361-e379 [PMID: 33798711 DOI: 10.1016/j.cgh.2021.03.034]

36 **Yang E**, Panaccione N, Whitmire N, Dulai PS, Vande Casteele N, Singh S, Boland BS, Collins A, Sandborn WJ, Panaccione R, Battat R. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Aliment Pharmacol Ther* 2020; **51**: 1031-1038 [PMID: 32329532 DOI: 10.1111/apt.15719]

37 **Glassner K**, Oglat A, Duran A, Koduru P, Perry C, Wilhite A, Abraham BP. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. *J Dig Dis* 2020; **21**: 264-271 [PMID: 32324969 DOI: 10.1111/1751-2980.12867]

38 **Sandborn WJ**, Lee SD, Tarabar D, Louis E, Klopocka M, Klaus J, Reinisch W, Hébuterne X, Park DI, Schreiber S, Nayak S, Ahmad A, Banerjee A, Brown LS, Cataldi F, Gorelick KJ, Cheng JB, Hassan-Zahraee M, Clare R, D'Haens GR. Phase II evaluation of anti-MAdCAM antibody PF-00547659 in the treatment of Crohn's disease: report of the OPERA study. *Gut* 2018; **67**: 1824-1835 [PMID: 28982740 DOI: 10.1136/gutjnl-2016-313457]

39 **Kofla-Dłubacz A**, Akutko K, Krzesiek E, Jamer T, Braksator J, Grębska P, Pytrus T, Stawarski A. Selective Forms of Therapy in the Treatment of Inflammatory Bowel Diseases. *J Clin Med* 2022; **11** [PMID: 35207271 DOI: 10.3390/jcm11040994]

40 **Alayo QA**, Fenster M, Altayar O, Glassner KL, Llano E, Clark-Snustad K, Patel A, Kwapisz L, Yarur AJ, Cohen BL, Ciorba MA, Thomas D, Lee SD, Loftus EV Jr, Fudman DI, Abraham BP, Colombel JF, Deepak P. Systematic Review With Meta-analysis: Safety and Effectiveness of Combining Biologics and Small Molecules in Inflammatory Bowel Disease. *Crohns Colitis 360* 2022; **4**: otac002 [PMID: 35310082 DOI: 10.1093/crocol/otac002]

41 **Sands BE**, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, Goldblum R, Harrigan R, Hilton D, Hanauer SB. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis* 2007; **13**: 2-11 [PMID: 17206633 DOI: 10.1002/ibd.20014]

42 **Dolinger MT**, Spencer EA, Lai J, Dunkin D, Dubinsky MC. Dual Biologic and Small Molecule Therapy for the Treatment of Refractory Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2021; **27**: 1210-1214 [PMID: 33125058 DOI: 10.1093/ibd/izaa277]

43 **Kwapisz L**, Raffals LE, Bruining DH, Pardi DS, Tremaine WJ, Kane SV, Papadakis KA, Coelho-Prabhu N, Kisiel JB, Heron V, Faubion WA, Loftus EV Jr. Combination Biologic Therapy in Inflammatory Bowel Disease: Experience From a Tertiary Care Center. *Clin Gastroenterol Hepatol* 2021; **19**: 616-617 [PMID: 32068149 DOI: 10.1016/j.cgh.2020.02.017]

44 **Mosli MH**, Sandborn WJ, Kim RB, Khanna R, Al-Judaibi B, Feagan BG. Toward a personalized medicine approach to the management of inflammatory bowel disease. *Am J Gastroenterol* 2014; **109**: 994-1004 [PMID: 24842338 DOI: 10.1038/ajg.2014.110]

45 **Hazlewood GS**, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology* 2015; **148**: 344-54.e5; quiz e14 [PMID: 25448924 DOI: 10.1053/j.gastro.2014.10.011]

46 **Zhao M**, Bendtsen F, Petersen AM, Larsen L, Dige A, Hvas C, Seidelin JB, Burisch J. Predictors of response and disease course in patients with inflammatory bowel disease treated with biological therapy-the Danish IBD Biobank Project: protocol for a multicentre prospective cohort study. *BMJ Open* 2020; **10**: e035756 [PMID: 32102828 DOI: 10.1136/bmjopen-2019-035756]

47 **Kennedy NA**, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, Thomas A, Nice R, Perry MH, Bouri S, Chanchlani N, Heerasing NM, Hendy P, Lin S, Gaya DR, Cummings JRF, Selinger CP, Lees CW, Hart AL, Parkes M, Sebastian S, Mansfield JC, Irving PM, Lindsay J, Russell RK, McDonald TJ, McGovern D, Goodhand JR, Ahmad T; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019; **4**: 341-353 [PMID: 30824404 DOI: 10.1016/S2468-1253(19)30012-3]

48 **Vande Casteele N**, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, Simoens S, Rutgeerts P, Gils A, Vermeire S. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015; **148**: 1320-9.e3 [PMID: 25724455 DOI: 10.1053/j.gastro.2015.02.031]

49 **Cheifetz AS**, Abreu MT, Afif W, Cross RK, Dubinsky MC, Loftus EV Jr, Osterman MT, Saroufim A, Siegel CA, Yarur AJ, Melmed GY, Papamichael K. A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease. *Am J Gastroenterol* 2021; **116**: 2014-2025 [PMID: 34388143 DOI: 10.14309/ajg.0000000000001396]

50 **Flamant M**, Roblin X. Inflammatory bowel disease: towards a personalized medicine. *Therap Adv Gastroenterol* 2018; **11**: 1756283X17745029 [PMID: 29383027 DOI: 10.1177/1756283X17745029]

51 **Schmitt H**, Billmeier U, Dieterich W, Rath T, Sonnewald S, Reid S, Hirschmann S, Hildner K, Waldner MJ, Mudter J, Hartmann A, Grützmann R, Neufert C, Münster T, Neurath MF, Atreya R. Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. *Gut* 2019; **68**: 814-828 [PMID: 29848778 DOI: 10.1136/gutjnl-2017-315671]

52 **Feuerstein JD**, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology* 2017; **153**: 827-834 [PMID: 28780013 DOI: 10.1053/j.gastro.2017.07.032]

53 **Biasci D**, Lee JC, Noor NM, Pombal DR, Hou M, Lewis N, Ahmad T, Hart A, Parkes M, McKinney EF, Lyons PA, Smith KGC. A blood-based prognostic biomarker in IBD. *Gut* 2019; **68**: 1386-1395 [PMID: 31030191 DOI: 10.1136/gutjnl-2019-318343]

54 **Lee JC**, Lyons PA, McKinney EF, Sowerby JM, Carr EJ, Bredin F, Rickman HM, Ratlamwala H, Hatton A, Rayner TF, Parkes M, Smith KG. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. *J Clin Invest* 2011; **121**: 4170-4179 [PMID: 21946256 DOI: 10.1172/JCI59255]

55 BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016 [PMID: 27010052]

56 **Gisbert JP**, Chaparro M. Predictors of Primary Response to Biologic Treatment [Anti-TNF, Vedolizumab, and Ustekinumab] in Patients With Inflammatory Bowel Disease: From Basic Science to Clinical Practice. *J Crohns Colitis* 2020; **14**: 694-709 [PMID: 31777929 DOI: 10.1093/ecco-jcc/jjz195]

57 **Beltrán B**, Iborra M, Sáez-González E, Marqués-Miñana MR, Moret I, Cerrillo E, Tortosa L, Bastida G, Hinojosa J, Poveda-Andrés JL, Nos P. Fecal Calprotectin Pretreatment and Induction Infliximab Levels for Prediction of Primary Nonresponse to Infliximab Therapy in Crohn's Disease. *Dig Dis* 2019; **37**: 108-115 [PMID: 30149385 DOI: 10.1159/000492626]

58 **Verstockt B**, Verstockt S, Veny M, Dehairs J, Arnauts K, Van Assche G, De Hertogh G, Vermeire S, Salas A, Ferrante M. Expression Levels of 4 Genes in Colon Tissue Might Be Used to Predict Which Patients Will Enter Endoscopic Remission After Vedolizumab Therapy for Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2020; **18**: 1142-1151.e10 [PMID: 31446181 DOI: 10.1016/j.cgh.2019.08.030]

59 **Verstockt B**, Verstockt S, Dehairs J, Ballet V, Blevi H, Wollants WJ, Breynaert C, Van Assche G, Vermeire S, Ferrante M. Low TREM1 expression in whole blood predicts anti-TNF response in inflammatory bowel disease. *EBioMedicine* 2019; **40**: 733-742 [PMID: 30685385 DOI: 10.1016/j.ebiom.2019.01.027]

60 **Bek S**, Nielsen JV, Bojesen AB, Franke A, Bank S, Vogel U, Andersen V. Systematic review: genetic biomarkers associated with anti-TNF treatment response in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2016; **44**: 554-567 [PMID: 27417569 DOI: 10.1111/apt.13736]

61 **Sazonovs A**, Kennedy NA, Moutsianas L, Heap GA, Rice DL, Reppell M, Bewshea CM, Chanchlani N, Walker GJ, Perry MH, McDonald TJ, Lees CW, Cummings JRF, Parkes M, Mansfield JC, Irving PM, Barrett JC, McGovern D, Goodhand JR, Anderson CA, Ahmad T; PANTS Consortium. HLA-DQA1*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease. *Gastroenterology* 2020; **158**: 189-199 [PMID: 31600487 DOI: 10.1053/j.gastro.2019.09.041]

62 **Martin JC**, Chang C, Boschetti G, Ungaro R, Giri M, Grout JA, Gettler K, Chuang LS, Nayar S, Greenstein AJ, Dubinsky M, Walker L, Leader A, Fine JS, Whitehurst CE, Mbow ML, Kugathasan S, Denson LA, Hyams JS, Friedman JR, Desai PT, Ko HM, Laface I, Akturk G, Schadt EE, Salmon H, Gnjatic S, Rahman AH, Merad M, Cho JH, Kenigsberg E. Single-Cell Analysis of Crohn's Disease Lesions Identifies a Pathogenic Cellular Module Associated with Resistance to Anti-TNF Therapy. *Cell* 2019; **178**: 1493-1508.e20 [PMID: 31474370 DOI: 10.1016/j.cell.2019.08.008]

63 **Rajca S**, Grondin V, Louis E, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Paintaud G, Piver E, Allez M, Mary JY, Sokol H, Colombel JF, Seksik P. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. *Inflamm Bowel Dis* 2014; **20**: 978-986 [PMID: 24788220 DOI: 10.1097/MIB.0000000000000036]

64 **Magnusson MK**, Strid H, Sapnara M, Lasson A, Bajor A, Ung KA, Öhman L. Anti-TNF Therapy Response in Patients with Ulcerative Colitis Is Associated with Colonic Antimicrobial Peptide Expression and Microbiota Composition. *J Crohns Colitis* 2016; **10**: 943-952 [PMID: 26896085 DOI: 10.1093/ecco-jcc/jjw051]

65 **Shaw KA**, Bertha M, Hofmekler T, Chopra P, Vatanen T, Srivatsa A, Prince J, Kumar A, Sauer C, Zwick ME, Satten GA, Kostic AD, Mulle JG, Xavier RJ, Kugathasan S. Dysbiosis, inflammation, and response to treatment: a longitudinal study of pediatric subjects with newly diagnosed inflammatory bowel disease. *Genome Med* 2016; **8**: 75 [PMID: 27412252 DOI: 10.1186/s13073-016-0331-y]

66 **Aden K**, Rehman A, Waschina S, Pan WH, Walker A, Lucio M, Nunez AM, Bharti R, Zimmerman J, Bethge J, Schulte B, Schulte D, Franke A, Nikolaus S, Schroeder JO, Vandeputte D, Raes J, Szymczak S, Waetzig GH, Zeuner R, Schmitt-Kopplin P, Kaleta C, Schreiber S, Rosenstiel P. Metabolic Functions of Gut Microbes Associate With Efficacy of Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Diseases. *Gastroenterology* 2019; **157**: 1279-1292.e11 [PMID: 31326413 DOI: 10.1053/j.gastro.2019.07.025]

67 **Joossens M**, Huys G, Cnockaert M, De Preter V, Verbeke K, Rutgeerts P, Vandamme P, Vermeire S. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. *Gut* 2011; **60**: 631-637 [PMID: 21209126 DOI: 10.1136/gut.2010.223263]

68 **Nikolaus S**, Schulte B, Al-Massad N, Thieme F, Schulte DM, Bethge J, Rehman A, Tran F, Aden K, Häsler R, Moll N, Schütze G, Schwarz MJ, Waetzig GH, Rosenstiel P, Krawczak M, Szymczak S, Schreiber S. Increased Tryptophan Metabolism Is Associated With Activity of Inflammatory Bowel Diseases. *Gastroenterology* 2017; **153**: 1504-1516.e2 [PMID: 28827067 DOI: 10.1053/j.gastro.2017.08.028]

69 **Ding NS**, McDonald JAK, Perdones-Montero A, Rees DN, Adegbola SO, Misra R, Hendy P, Penez L, Marchesi JR, Holmes E, Sarafian MH, Hart AL. Metabonomics and the Gut Microbiome Associated With Primary Response to Anti-TNF Therapy in Crohn's Disease. *J Crohns Colitis* 2020; **14**: 1090-1102 [PMID: 32119090 DOI: 10.1093/ecco-jcc/jjaa039]

70 **Zwerina J**, Hayer S, Tohidast-Akrad M, Bergmeister H, Redlich K, Feige U, Dunstan C, Kollias G, Steiner G, Smolen J, Schett G. Single and combined inhibition of tumor necrosis factor, interleukin-1, and RANKL pathways in tumor necrosis factor-induced arthritis: effects on synovial inflammation, bone erosion, and cartilage destruction. *Arthritis Rheum* 2004; **50**: 277-290 [PMID: 14730626 DOI: 10.1002/art.11487]

71 **Labrijn AF**, Janmaat ML, Reichert JM, Parren PWHI. Bispecific antibodies: a mechanistic review of the pipeline. *Nat Rev Drug Discov* 2019; **18**: 585-608 [PMID: 31175342 DOI: 10.1038/s41573-019-0028-1]

72 **Peyrin-Biroulet L**, Demarest S, Nirula A. Bispecific antibodies: The next generation of targeted inflammatory bowel disease therapies. *Autoimmun Rev* 2019; **18**: 123-128 [PMID: 30572136 DOI: 10.1016/j.autrev.2018.07.014]

73 **Privitera G**, Pugliese D, Onali S, Petito V, Scaldaferri F, Gasbarrini A, Danese S, Armuzzi A. Combination therapy in inflammatory bowel disease - from traditional immunosuppressors towards the new paradigm of dual targeted therapy. *Autoimmun Rev* 2021; **20**: 102832 [PMID: 33866066 DOI: 10.1016/j.autrev.2021.102832]

74 **Vermeire S**, Sandborn WJ, Danese S, Hébuterne X, Salzberg BA, Klopocka M, Tarabar D, Vanasek T, Greguš M, Hellstern PA, Kim JS, Sparrow MP, Gorelick KJ, Hinz M, Ahmad A, Pradhan V, Hassan-Zahraee M, Clare R, Cataldi F, Reinisch W. Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase 2, randomised, double-

blind, placebo-controlled trial. *Lancet* 2017; **390**: 135-144 [PMID: 28527704 DOI: 10.1016/S0140-6736(17)30930-3]

75 **Spiess C**, Zhai Q, Carter PJ. Alternative molecular formats and therapeutic applications for bispecific antibodies. *Mol Immunol* 2015; **67**: 95-106 [PMID: 25637431 DOI: 10.1016/j.molimm.2015.01.003]

76 **van Schie KA**, Wolbink GJ, Rispens T. Cross-reactive and pre-existing antibodies to therapeutic antibodies--Effects on treatment and immunogenicity. *MAbs* 2015; **7**: 662-671 [PMID: 25962087 DOI: 10.1080/19420862.2015.1048411]

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